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August 30, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

RE: **Docket No.** 99D-1454
Draft Guidance for Industry on Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products; Chemistry, Manufacturing, and Controls Documentation

Dear Administrator:

Kos Pharmaceuticals, Inc. (Kos), and Aeropharm Technology, Inc. (ATI), a wholly owned subsidiary of Kos, is submitting comments to FDA in response to the request published in the June 2, 1999 Federal Register regarding the *Draft* Guidance for *Industry, Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products; Chemistry, Manufacturing, **and** Controls Documentation,* Docket No. 99D-1454. General comments and a listing of suggested changes to the guidance document are attached.

Kos Pharmaceuticals, Inc. greatly appreciates and supports FDA's efforts to develop a Guidance for Industry for Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products. If you have any questions concerning the comments, please call me at (305) 5 12-7039. Thank you again for the opportunity to provide FDA with our comments and suggestions.

Sincerely,

JoAnn H. Smith
Regulatory Affairs, Associate

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99D-1454

SECTION I - INTRODUCTION

Kos fully agrees with the Agency's position as stated in the Introduction to the Draft Guidance, that "alternative approaches may be used." We believe adherence to this concept is essential if this, or any guidance, is to be useful and stand the test of time.

SECTION II - BACKGROUND

Kos suggests that the Draft Guidance would be strengthened if the provision regarding alternate approaches were further emphasized in this background section and throughout the document. The diversity of products and devices and the prospect of evolving, new technology platforms for still newer products in the future will be best served with a Guidance that is not unnecessarily restrictive.

With respect to sterility, Kos would like to point-out that nasal sprays are not currently classified as sterile. Kos suggests that a statement indicating that nasal sprays are not required to be sterile be added to Section A of the Background and that any other references to nasal sprays as sterile products be deleted from or clarified in the guidance (e.g., line 106). Also, please add a statement that only inhalation solutions for nebulization should be sterile.

SECTION III – DRUG PRODUCT

Section III (F) (1) (g) – Spray Content Uniformity

In this section, the Guidance document establishes a single, all encompassing specification for spray content uniformity that does not provide for considerations relative to drug concentration, analytical test method sensitivity, and limit of quantitation attributes. The Guidance document also does not appear to allow for relevant development or production data to be used to characterize these products. Criteria set forth in the compendia for spray content uniformity testing of nasal spray solutions to which this class of products belongs (See *Draft-in-Process on Testing Aerosols <601> Pharmacopeial Forum,* Volume 24, Number 5) deserve some consideration based upon history and performance of these products. Kos thus recommends that the Agency establish a process by which a spray content uniformity specification could be determined, on a product-by-product basis, in light of relevant product-specific development and manufacturing data. Kos also believes that the Guidance document would be most useful and meaningful to industry if it focuses on types of testing and methods of data evaluation rather than on specifics of results that must be achieved during development and commercial manufacture of these products. Development tests and methods should not in all cases become the regulatory (release) specifications.

Kos recommends that the Draft Guidance include a statement of principles that should be taken into account when setting specifications. We also recommend that

the Agency consider adopting the draft ICH position on specifications, which is presented below for the Agency's convenience:

> *Specifications are one part of a total control strategy for the drug substance and drug product designed to ensure product quality and consistency. Other parts of this strategy include thorough product characterization during development upon which specifications are based, adherence to good manufacturing practices (GMPs), and a validated manufacturing process, e.g., raw material testing, in-process testing, stability testing.*
>
> *Specifications are chosen to confirm the quality of the drug substance and drug product rather than to establish full characterization, and should focus on those characteristics found to be useful in ensuring the safety and efficacy of the drug substance and drug product.*
>
> *When a specification is first proposed, justification should be presented for each procedure and each acceptance criterion included. The justification should refer to relevant development data, pharmacopeial standards, test data for drug substances and drug products used in toxicology and clinical studies, and results from accelerated and long term stability studies, as appropriate. Additionally, a reasonable range of expected analytical and manufacturing variability should be considered. It is important to consider all of this information.*
>
> *(*Q6A *Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances, 62* Fed Reg 62890, 62891-62892*).*

Also, within the Guidance document the number of containers to be tested is clearly stated, but not the number of sprays per unit. Guidelines for determining the variability within a container are not clearly stipulated in this section. Additionally, as the testing required under Section h "Spray Content Uniformity Through Container Life" gives a more accurate account of variability within the unit, testing of a multiple number of sprays from a container to satisfy Section g "Spray Content Uniformity" might be redundant in light of the requirements outlined in Section h.

Section III (F) (1) (i) – Spray Pattern and Plume Geometry

The Guidance states that "spray pattern testing should be performed on a routine basis as a quality control for release of the drug product." Kos suggests that spray pattern testing should be conducted as an incoming component test, not as a drug product release test.

In this section the Guidance stipulates that "the proposed test procedure for spray pattern, including analytical sampling plans, should be provided in detail to allow duplication by Agency laboratories." Kos suggests that the sampling plan to be used be further discussed since routine testing of spray pattern based on current statistical sampling tables may require an inordinate amount of resources. Testing a finite number of units sampled throughout the lot may be more feasible and lead to analogous conclusions.

Section III (1) (I) – Microscopic Evaluation (Nasal Suspensions)

The Draft Guidance includes microscopic evaluation as a release and stability-testing requirement. While microscopy may be used in the early stages of product design and development to confirm other product characterization findings, finished product attributes such as particle size are better controlled by other test methods.

Section III (F) (1) (n) – Microbial Limits

The Guidance states that "appropriate testing should show that the drug product does not support the growth of microorganisms and that microbiological quality is maintained throughout the expiration dating period." To show that the drug product does not support the growth of microorganisms may require microbial challenge studies alluded to in Section 0 "Preservatives Effectiveness." If this is the case, then what has to be done differently with sprays that contain a preservative as compared to those that do not?

Section III (F) (1) (p) – Net Content and Weight Loss (Stability)

The Guidance requires that the drug product should be stored in an upright and inverted or upright and horizontal position to assess weight loss. Kos requests that this requirement be deleted from the Guidance document as pumps in general tend to leak in an inverted or horizontal position. Labeling to store upright should be sufficient.

Section III (F) (1) (q) – Leachables (Stability)

Control of leachables is more appropriate at the component or bulk material level rather than on the product. Kos believes that a correlation between component levels and product levels should be evaluated during development. In addition, if levels are consistently well below the threshold of any safety concern, such testing may be eliminated altogether. We thus recommend not using leachables as a confirmation of composition or process compliance during manufacture of components or product, which falls more appropriately in the realm of cGMP.

Section III (G) – Container Closure System

This section stipulates that “for device-metered nasal or inhalation spray drug products designed for use with replaceable reservoirs, the device should be specific for the intended formulation reservoir only and should not allow use of an alternate reservoir that contains a different formulation.” Insuring that a patented delivery can only be used for one product may prove difficult if not impossible. Kos does not understand the justification for such a requirement (it is analogous to requiring that a hypodermic needle be used exclusively for one product only). Labeling against use with other products should suffice.

Line 855 of this section uses the word “precise.” Kos suggests that a definition of the word “precise” be included in the Glossary of Terms, or use of the phrase “generally accepted industrial specifications” be used instead of the word “precise”.

In regards to the requirement for toxicological evaluation of extractables, would a literature review be acceptable or are animal tests required?

Section III (G) (1) – Source, Chemical Composition, and Physical Dimensions

In this section, the Guidance indicates that critical components are defined to include protective packaging such as shrink-wrap or cartons. The Guidance also requires references to indirect food additive regulations for these components. As the drug product does not come in contact with secondary packaging components, Kos believes that this requirement is unnecessary.

Section III (G) (3) – Routine Extraction

The section on Routine Extraction requires that “an extraction test should be performed on every incoming component batch using water and other suitable solvents selected from control extraction studies, to determine the individual and total extractables.” Kos would like to note that water typically does not extract well. Water extraction is assayed in the developmental phase and water extraction should not be considered a routine test if nothing is found during developmental characterization.

Within this section of the Guidance the term “very low” is used. Kos believes that this term needs to be explained in detail so that industry will better understand what exactly would be considered “very low”.

Section III (G) (4) – Acceptance Criteria

The Guidance states that specifications for each component of the pump are required. Typically, individual pump components are not controlled at the drug manufacturer level, a pump is received and released as a unit. Individual component specifications are included in the supplier’s DMF.

Also, line 954 states that "data should be collected using defined actuation parameters (e.g., force, speed, hold and return times)." This statement implies the requirement of using an automated pump testing apparatus. Please clarify.

This section states that "a reduced acceptance testing schedule may be considered once the applicant establishes the reliability of the supplier's test results." Would once-a-year be acceptable as a reduced testing schedule?

Section III (H) (1) (d) – Test Storage Conditions

With respect to the statements concerning drug product storage under controlled room temperature conditions in semi-permeable packaging, please define semi-permeable or specify additional resins that FDA would consider as semi-permeable.

Section III (H) (1) (i) – Expiration Dating Period

This section states that "expiration dating should be based upon full shelf-life stability studies of at least three batches." Kos believes that l-year shelf-life data plus data from testing at accelerated stability conditions for 6 months should also be acceptable.

SECTION IV – DRUG PRODUCT CHRACTERIZATION STUDIES

Section IV (C) – Temperature Cycling

The Guidance states that "periodically throughout the study, at the end of a predetermined number of cycles, the samples should analyzed for appropriate parameters . . . test parameters for cycling studies should include .,, sterility and functionality of pump components." While the sterility of the drug product can be assured, the drug product will come into contact with pump components that may or may not be sterile depending on operator handling.

Section IV (F) – Device Ruggedness

This section requires dropping and shaking units to assess performance characteristics. These parameters need to be clearly defined (i.e., shake for two minutes on a shaker table at a given setting). If MIL standards are acceptable, these should be referenced.

SECTION V – LABELING CONSIDERATIONS

See comments in Section III F (1) (p) and Section G.

GENERAL COMMENTS

Consistency with Other Relevant Standards and Practices

There are several areas where the Draft Guidance may not be entirely consistent with other relevant standards (e.g., regulations and guidances) and practices. We believe it is important to maintain consistency with these other standards. We recommend that the Agency modify the Draft Guidance to make it more consistent with other relevant standards and practices. For example:

- The Draft Guidance makes several references to *product consistency, future batch-to-batch consistency,* and *reproducibility.* However, no information is provided to allow a quantitative or numerical approach to defining "consistency" or to determine when "reproducibility" has been violated. There are a number of scientifically recognized statistical and other quality control methods applicable to these products that are well accepted within the industry. We recommend that the Draft Guidance be amended to address in detail the use of these concepts and procedures to determine specifications.

CONCLUSION

Kos strongly supports the development of a Guidance document for Industry on Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products and appreciates the Agency's efforts in developing the current Draft Guidance. Given the variety and complexity of formulations and devices in this drug delivery technology area, Kos recognizes the difficulties and challenges present in the development of a single guidance document that adequately covers this range of diverse products. Kos also recognizes the value to industry of a guidance of this type, and believes it is important that this guidance be written in a way that recognizes and incorporates the diversity of products represented by this class of pharmaceuticals.

Kos believes this will clarify for industry, what aspects of pharmaceutical performance and quality the Agency considers important to control. In addition, a general Guidance document will help industry understand the reasoning behind the Agency's views and the Agency's expectations for new products. Further, when

product attributes and technical issues dictate alternate approaches, developers can easily focus their interactions with the Agency on those specific issues.

We hope our comments will be of value to the Agency and we look forward to the ultimate publication of a Final Guidance that will effectively serve the current and future needs of the Nasal Spray and Inhalation products industries.

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